

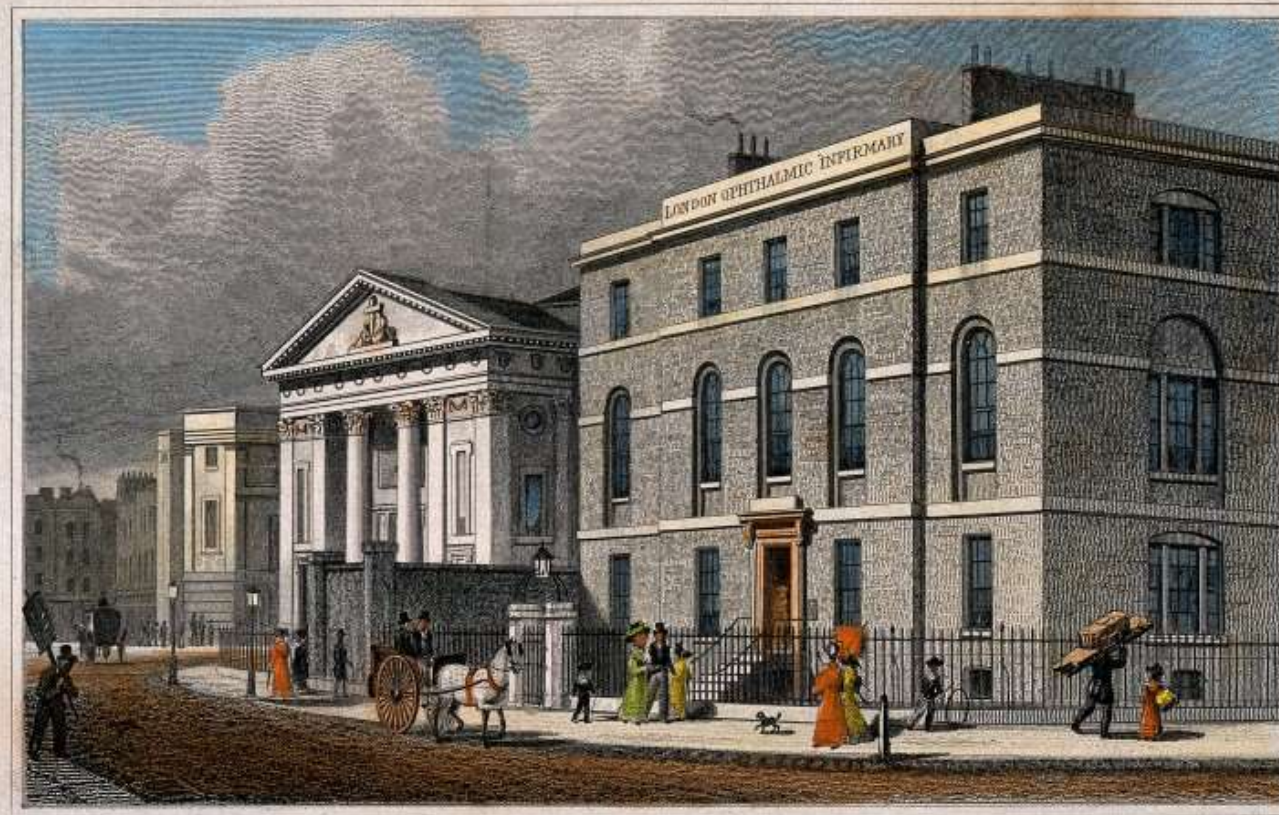
What's NEWish in diabetic retinopathy prevention, diagnosis, and treatment (innovation & tech?)

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Moorfields, 19th Century



Drawn by Thos. H. Shepherd.

Engraved by R. Aron.

LONDON OPHTHALMIC INFIRMARY, &c. FINSBURY.

Moorfields, 21st Century

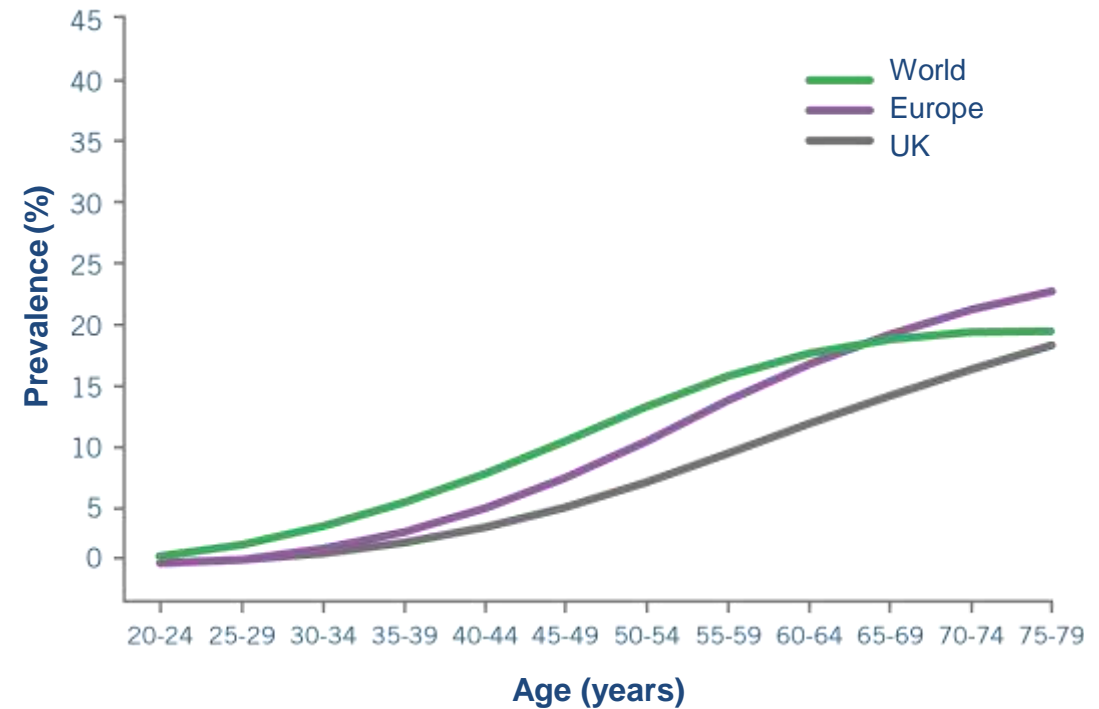


The Next Generation



Diabetes in the UK

- In 2015, there were an estimated 3.8 million adults with diabetes¹
 - Almost 1 million people were estimated to have undiagnosed diabetes
- By 2035, diabetes prevalence is expected to increase to 4.9 million¹



UK prevalence of diabetes vs European and global estimates (2013)²

1. Public Health England. Diabetes Prevalence Model. 2016. 2. International Diabetes Federation. IDF Diabetes Atlas: 6th Edition. 2013.

Epidemiology in the UK

Diabetic retinopathy

Of 3569 individuals screened within 6 months of T2DM diagnosis:¹

- 29.1% had background retinopathy (in one eye or both eyes)
- 2.3% had referable retinopathy

Prevalence of treatable DMO

United Kingdom National Ophthalmology Database Study of ~24,000 patients with diabetes²

CSMO
13.9%

**Non-centre
involving CSMO**
6.5%

**Centre involving
DMO**
7.4%

T2DM = Type 2 diabetes mellitus; DMO = Diabetic macular oedema; CSMO = Clinically significant macular oedema

1. Scanlon PH, et al. Diabet Med. 2014;31(4):439–442; 2. Keenan TD, et al. Eye. 2013;27(12):1397–1404.



Ophthalmology
Focused on you

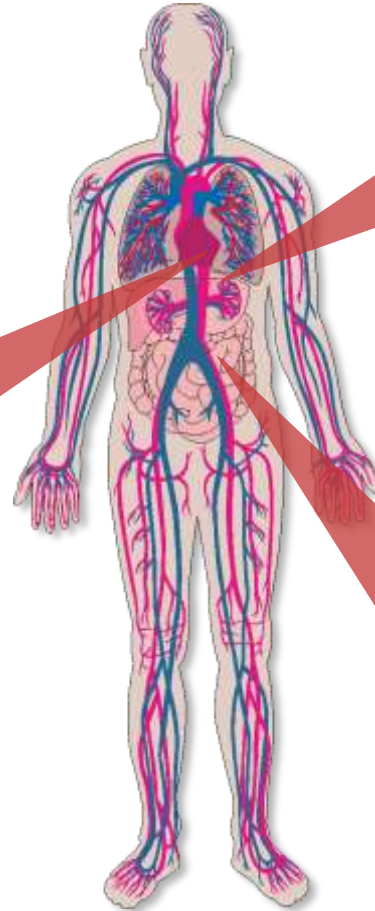
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Risk factors

Risk factors¹

Modifiable:

- Diabetic control / HbA1c
- Glycaemia
- Blood pressure
- Lipid levels
- BMI
- Vitamin D



Non-modifiable:

- Genetic factors
- Duration of diabetes
- Gender

Additional factors:

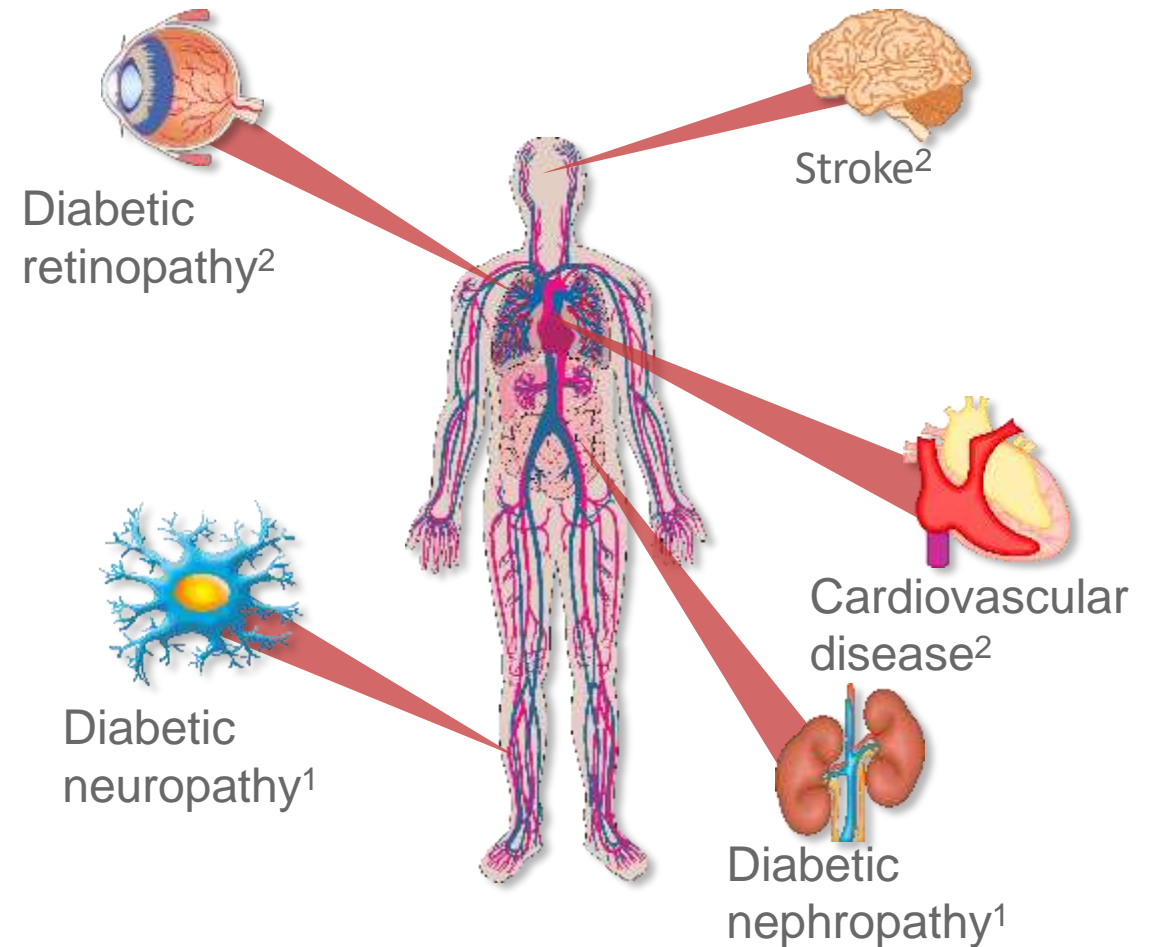
- Carotid arterial disease
- Pregnancy
- Renal impairment
- Smoking

HbA1c = Glycated haemoglobin.

1. RCOphth, Diabetic Retinopathy Guidelines, Dec 2012.

Co-morbidities²

- Comorbidity should be considered in the treatment of patients with diabetes¹
- There are significant levels of increased comorbidity in patients with DR¹
- Depression has also been shown to be more prevalent in the diabetic population compared to the non-diabetic population¹

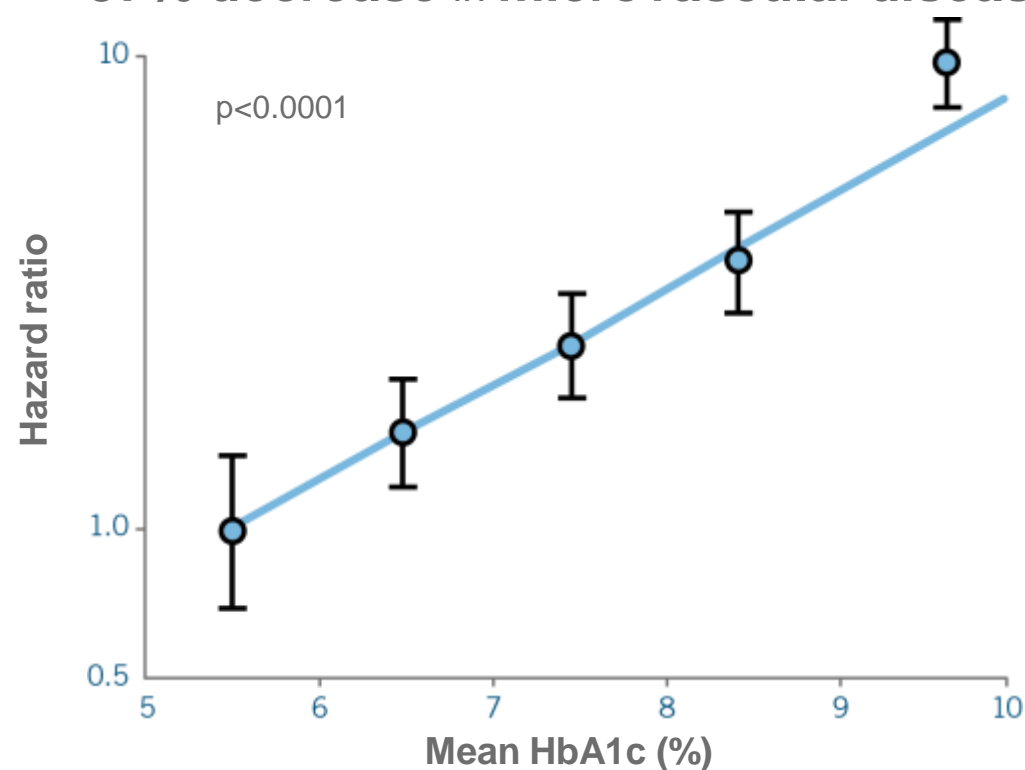


DR = Diabetic retinopathy.

1. RCOphth, Diabetic Retinopathy Guidelines, Dec 2012. 2. Centers for Disease Control and Prevention, National Diabetes Fact Sheet, 2011.

Managing HbA1c to reduce the risk of retinopathy¹

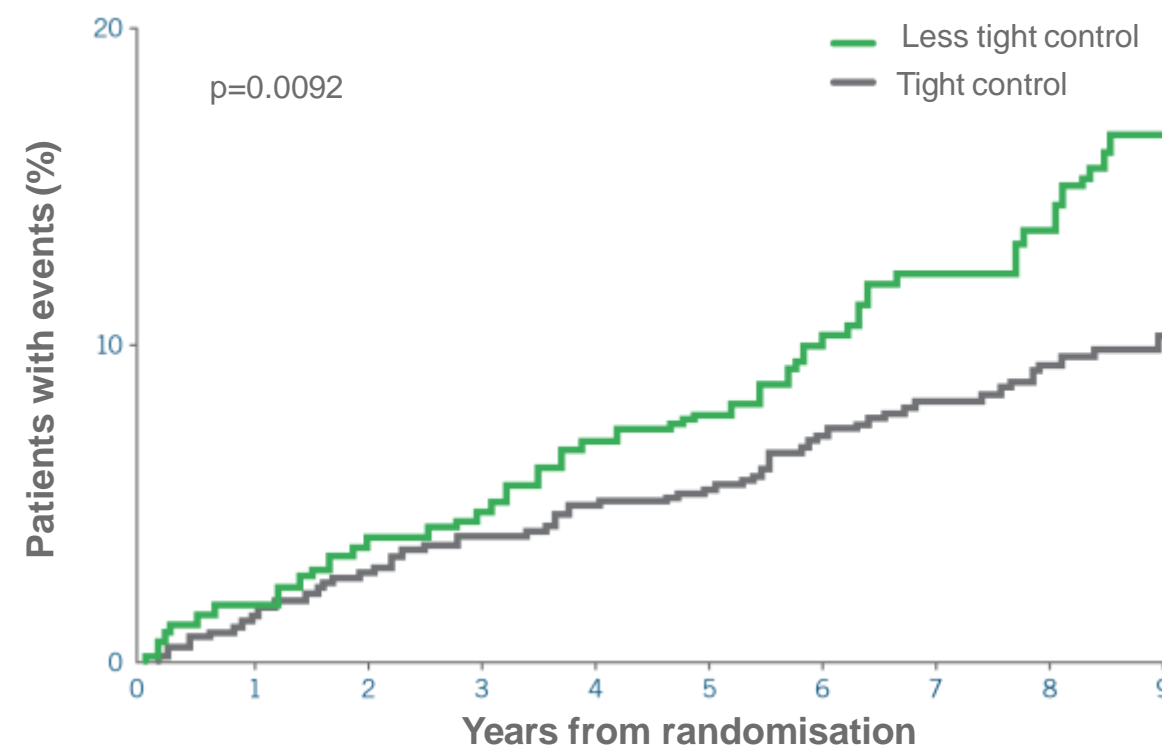
A **1% reduction** in HbA1c is associated with a **37% decrease** in **microvascular disease**



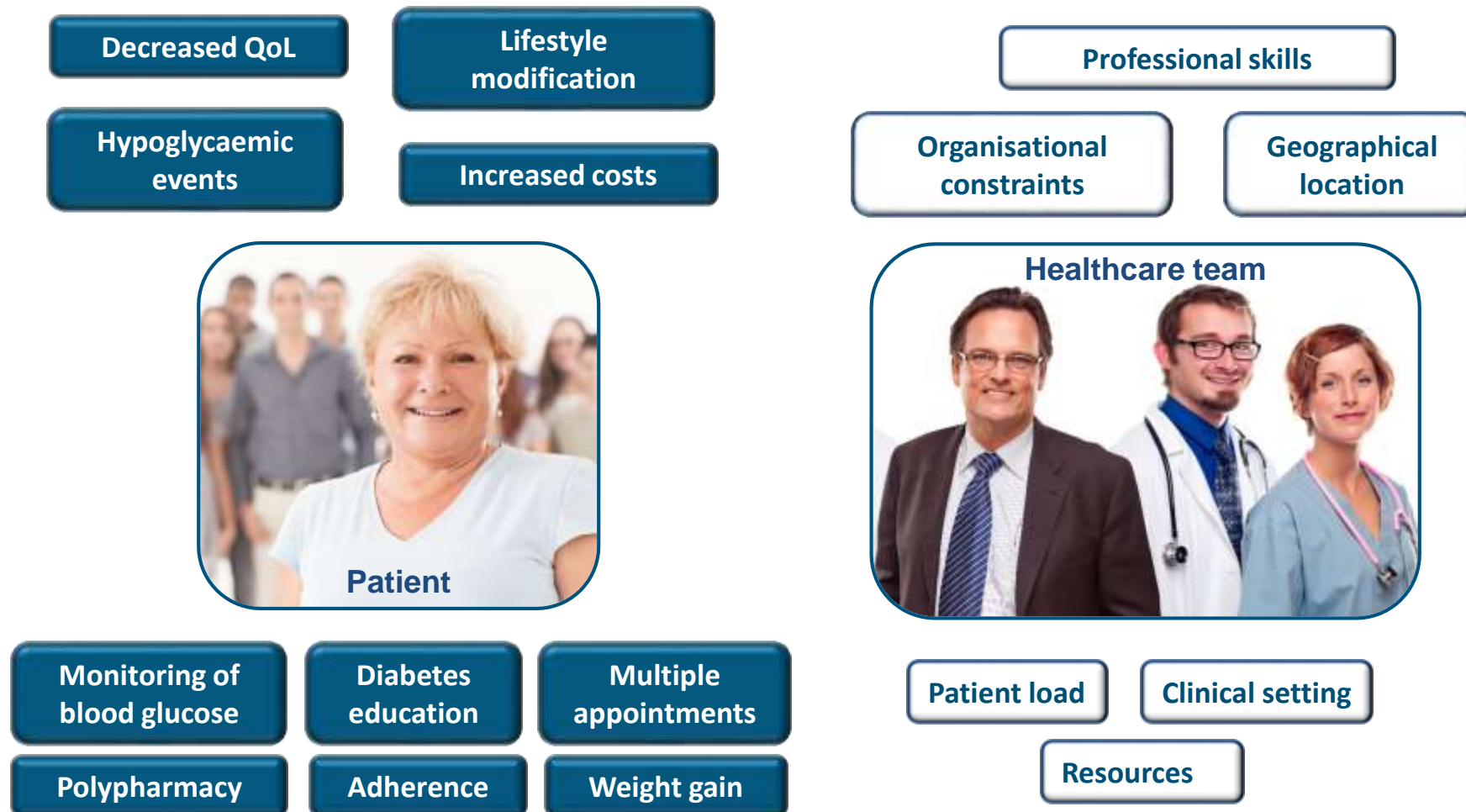
UKPDS: Hazard ratios (95% CI) as estimate of association between mean HbA1c and microvascular end points (mostly requirement for photocoagulation)

Managing blood pressure to reduce the risk of retinopathy²

Intensive blood pressure control (144/82 mm Hg) is associated with a **37% decrease** in **microvascular endpoints**



UKPDS: Proportion of patients who developed microvascular endpoints (mostly requirement for photocoagulation)



Innovation in Diabetes Eye Care

Role of the diabetes nurse specialist in eye department

- Health promotion & education
- Multispecialty working local physicians
- Bespoke counselling new patients & follow up
- Training & Development staff – diabetes care

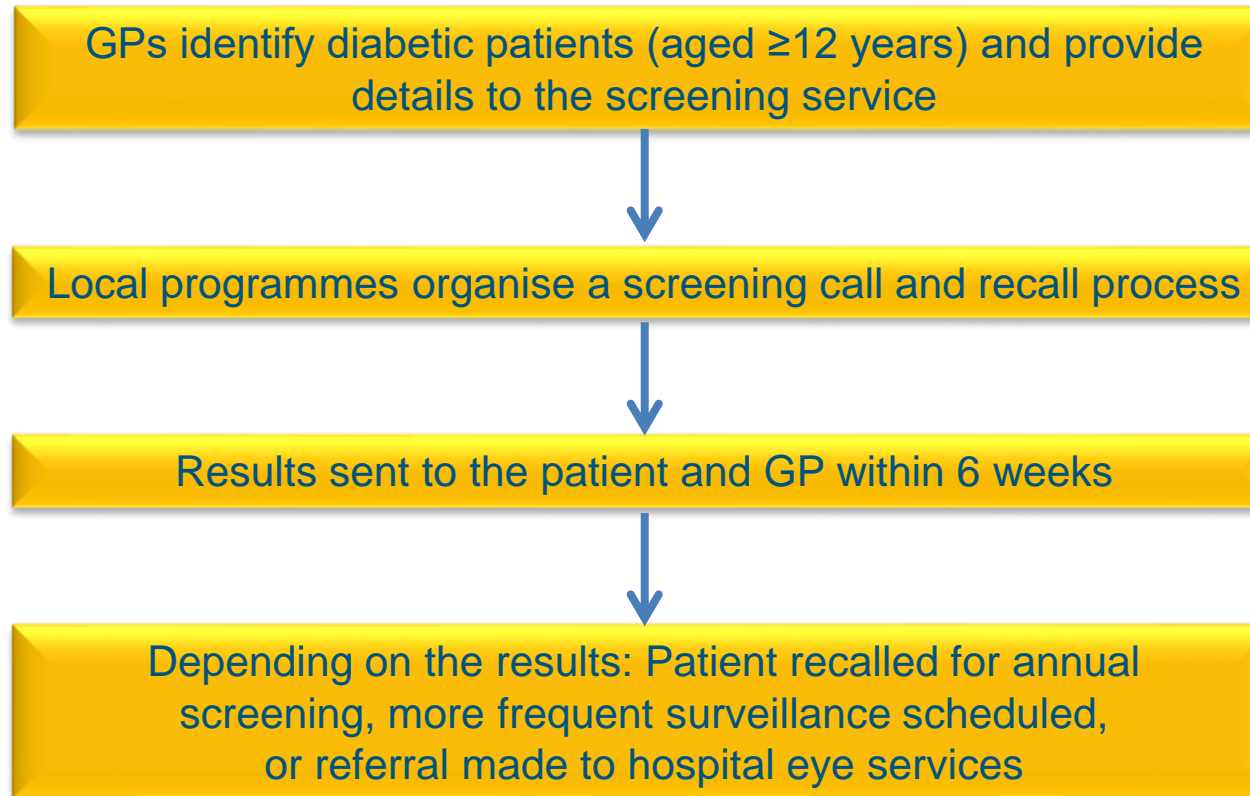
Diabetic Eye Passport innovation: summary

- App – smart phones
- Treatment response measurements
- BCVA summary
- DVLA regulations
- Injection appointment reminders
- Interpretation

BCVA: Best corrected visual acuity.



Community Based Retinal Screening



Diabetic retinopathy screening service

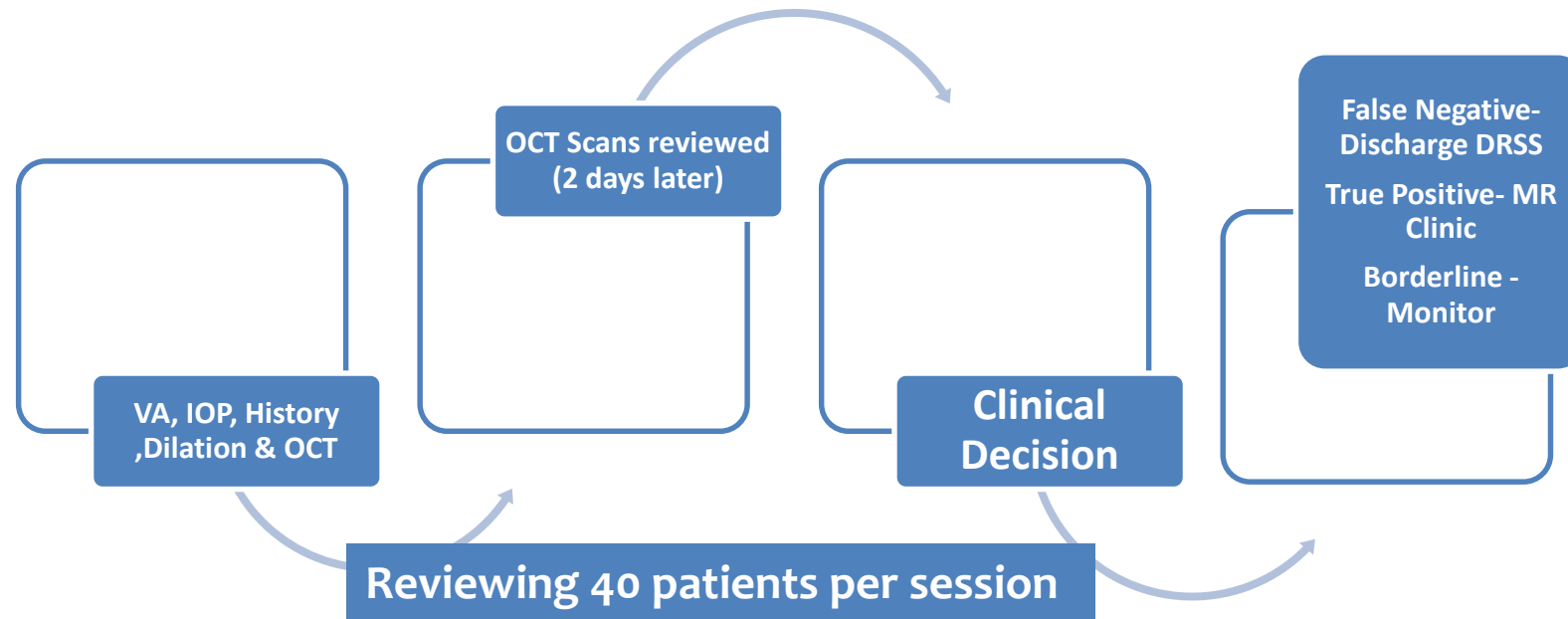
- * Fundus photography system carried out by Nurse/Optometrists/Technician
- * Screener subsequently examine & grade the images for evidence of DR lesions
- * Images graded by Nurse/Optometrists
- * Patients with sight threatening disease correctly identified by graders and follow NSC guidelines



Enhanced Digital Surveillance Service:

- Designed as high patient throughput
 - Minimal clinician contact
 - Maximising Capacity
- Technological advances – ophthalmic imaging



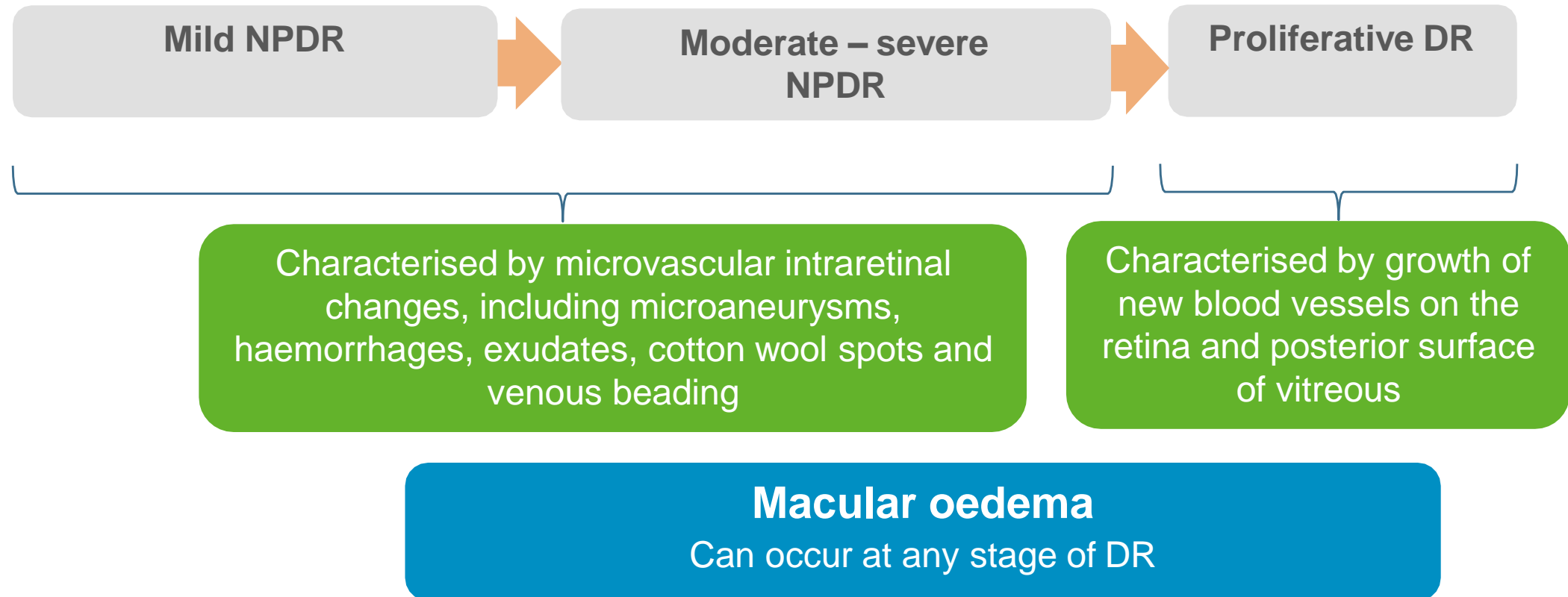


Digital Innovation and Diabetes Eye care

- Low Cost
- Digital Imaging
- Automated Grading
- Future AI application
- Shorter clinic Visits
- Digital apps; VA self check, symptoms self monitoring and appointment reminders

Progression and classification of DR^{1,2}

- Classified into different stages of severity of its progression



NDPR = Non-proliferative diabetic retinopathy.

1. Wu L, et al. World J Diabetes. 2013;4(6):290–294; 2. Stitt AW, et al. Prog Retin Eye Res. 2016;51:156–186.

Diabetic retinopathy

BDR



Pre-proliferative DR



PDR



BDR = Background diabetic retinopathy.
Images courtesy of Nigel Kenawy.

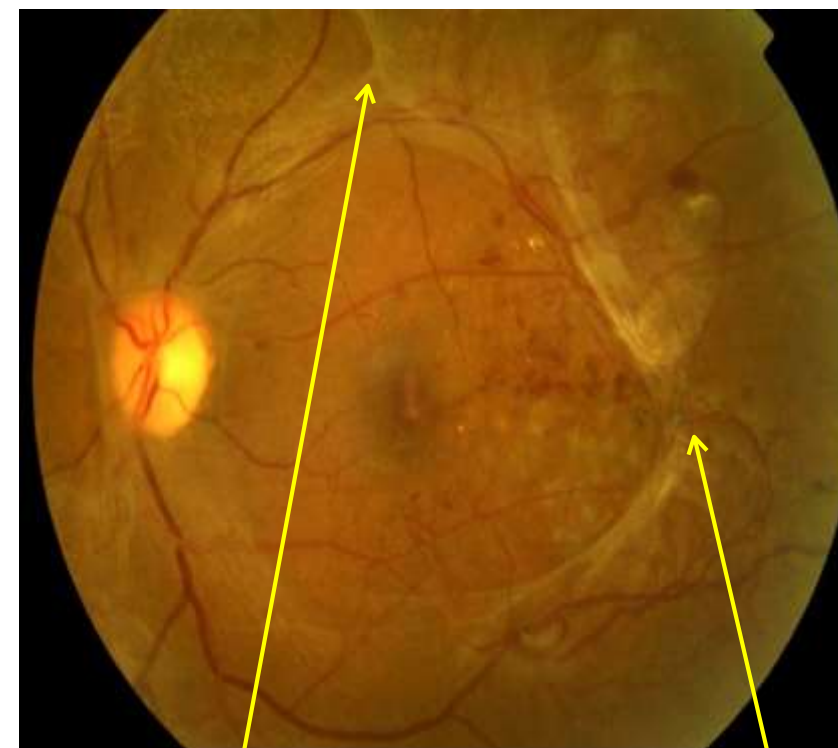
Proliferative diabetic retinopathy



Fibrosis &
traction

NVD
NVE

NVE



Fibrosis &
traction

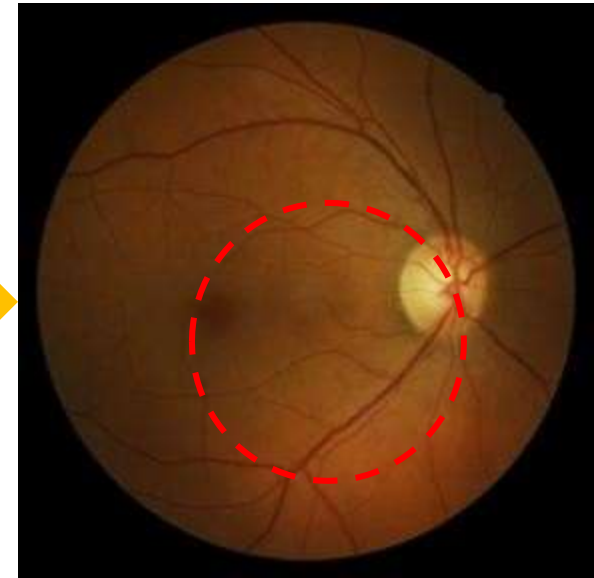
NVE

NVD = neovascularisation of the disc; NVE = neovascularisation elsewhere.

Why is DMO so important?

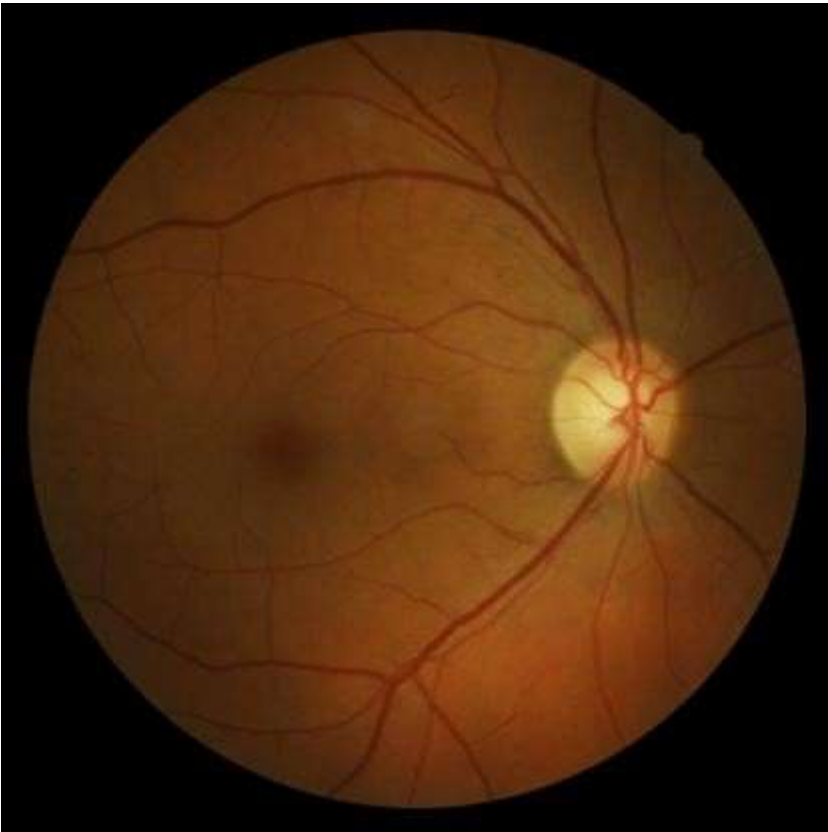
- The macula is responsible for central vision.
- Diabetic macular oedema may be asymptomatic at first. As the oedema moves in to the fovea (the center of the macula) the patient will notice blurry central vision. The ability to read and recognise faces will be compromised.

Macula
Fovea



The differences

Normal



Macular oedema



Confirming diagnosis

- History taking
- Visual acuity
- Non invasive investigations
- Invasive investigations

“80% of the diagnosis made is based on the history alone”

Sir William Osler (1849-1919)





Diabetic eye disease Pathogenesis & Sight Loss

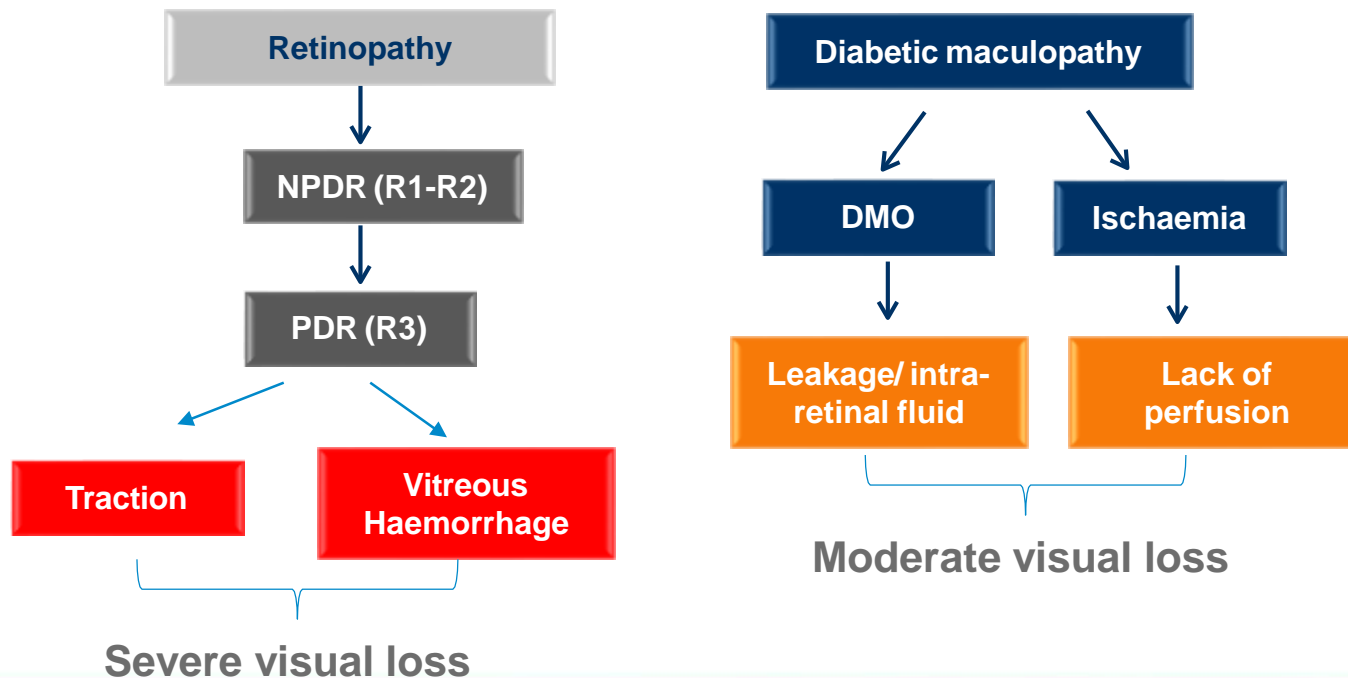
Why does retinopathy/maculopathy (DMO) occur?

- Ischaemia/ Angiogenesis
 - NVE/NVD/rubeosis (R3a)
- Leakage
- Exudates (M1)



What causes sight loss in diabetes?

- Diabetic retinopathy and maculopathy
- Diabetic retinopathy/maculopathy is the second leading cause of certifiable blindness among working-age adults in England and Wales – superseded by inherited retinal disorders¹
 - Attributed to the introduction of UK screening programmes and improved glycaemic control
- The condition can be well advanced before symptoms develop²
- Vision loss occurs through:³



Sight-threatening maculopathy

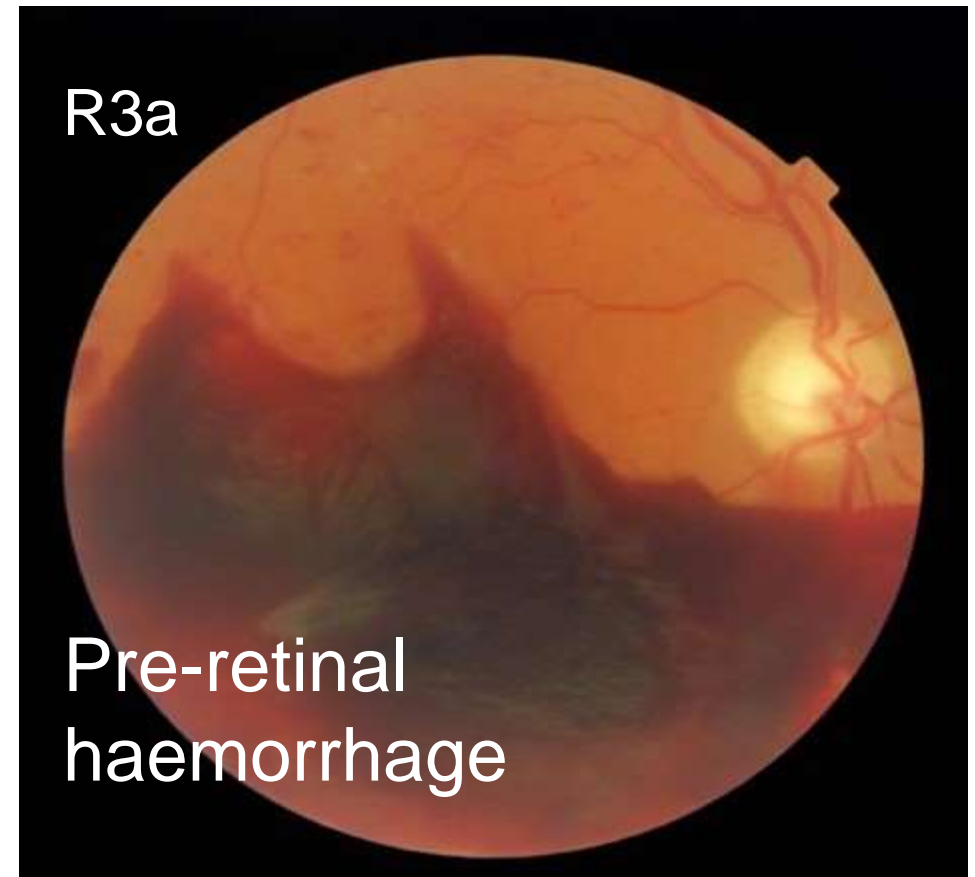
Image courtesy of Samantha Mann.

1. Liew G, et al. *BMJ Open*. 2014;4(2):e004015;

2. Clarke M. Diabetic Retinopathy. Dodson PM (ed.). Oxford University Press; 2008; 3. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines 2012.

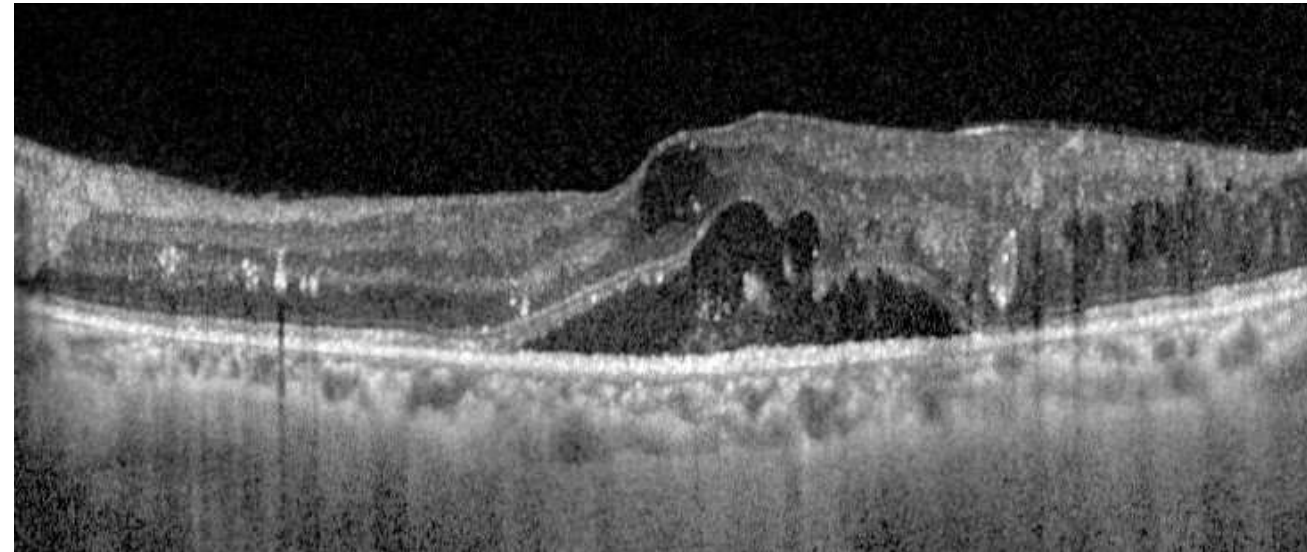
Causes of visual loss

- Advanced Proliferative with Vitreous haemorrhage/ Extensive pre-retinal haemorrhage



Causes of visual loss

- Extensive maculopathy/ DMO



CSME/DMO. Images courtesy of Samantha Mann



Investigation of retinopathy/ maculopathy

Investigation techniques

Slit-lamp Biomicroscopy

- 3-D view
- No permanent record
- Can identify CSME
- Poor correlation between OCT and CSME¹

Fluorescein Angiography

- Involves injection of fluorescein dye
- Can be wide field/ macular
- Identifies
 - **Focal oedema**
 - **Diffuse oedema**
 - **Ischaemic**
 - **Mixed**

OCT

- Has become routinely used to assess retinal thickness
- Treatment algorithms consider whether oedema is ³:
 - **Centre involving**
 - **Non-centre involving**

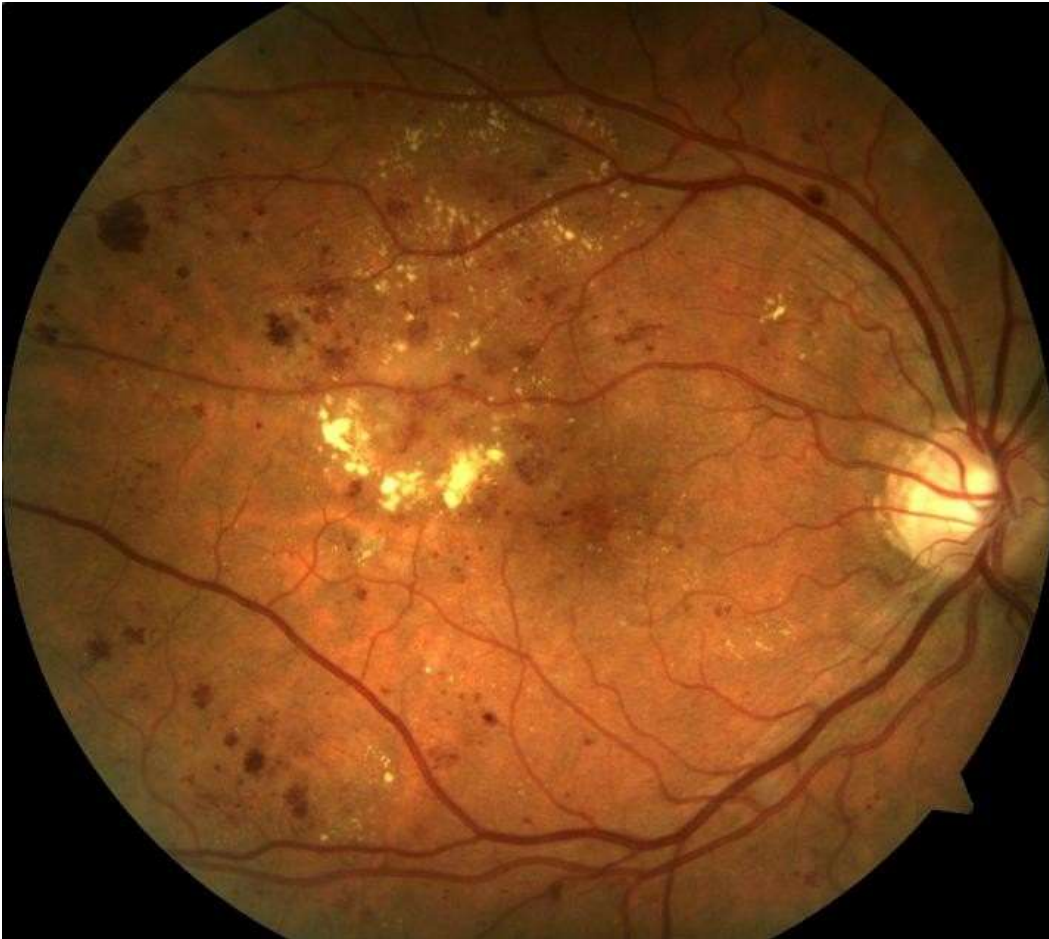
OCT-A

- Visualises the vasculature of the retina and choroid ⁴
- No need for dye
- Assesses foveal ischaemia
- Limited by artefacts and file size

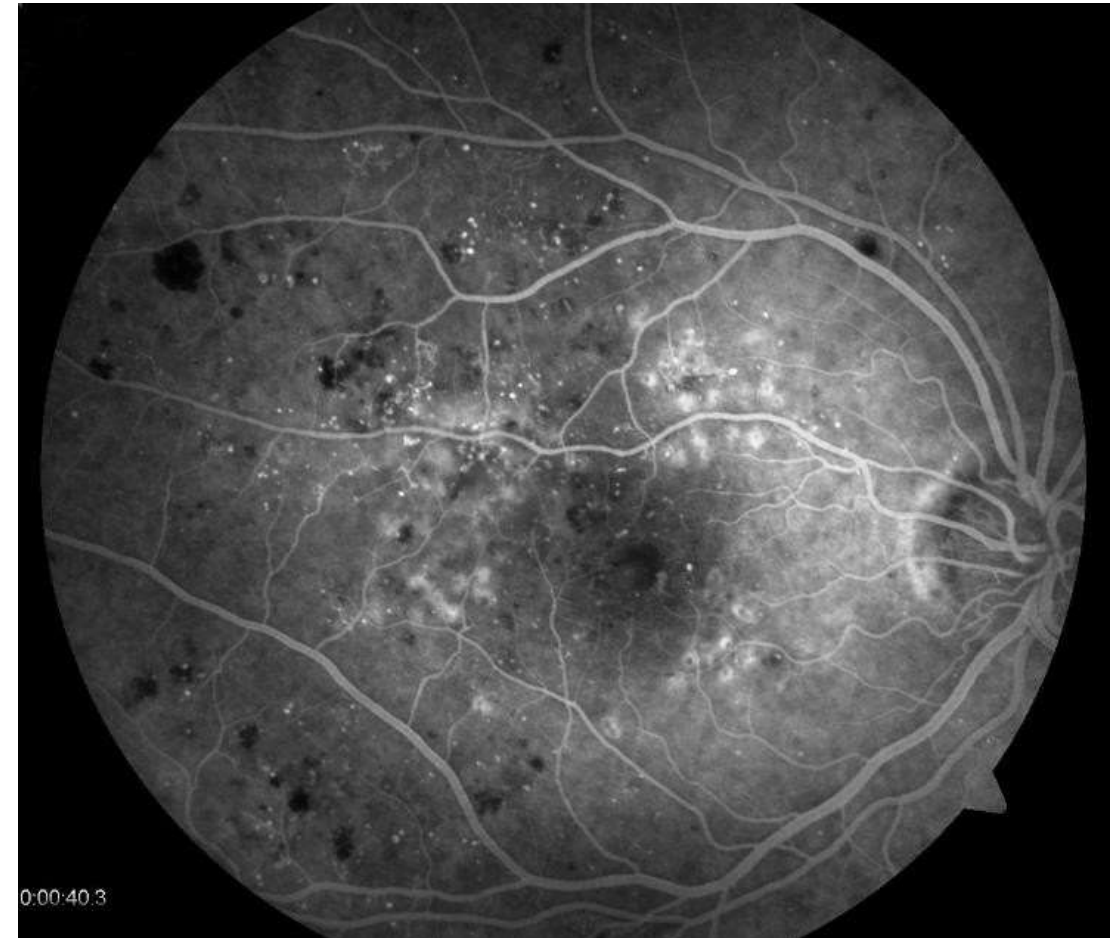
1. Wu L, et al. *World J Diabetes*. 2013;4(6):290–294; 2. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2012; 3. Ghanchi F. *Eye (Lond)*. 2013;27(2):285–287; 4. Kostenis A et al. *BJ Ophthalmol* 2016. Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research

CSMO

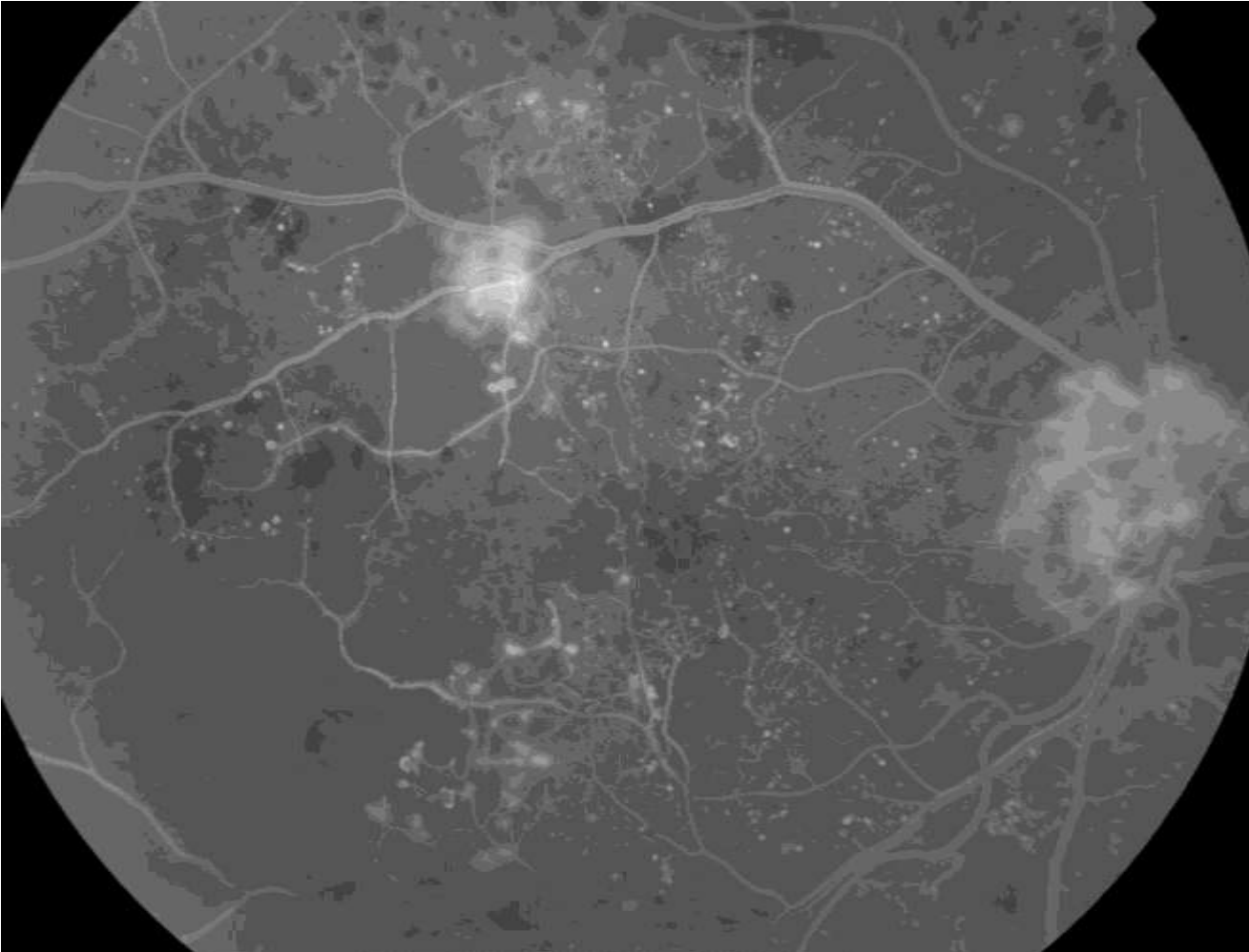
Fundus photograph



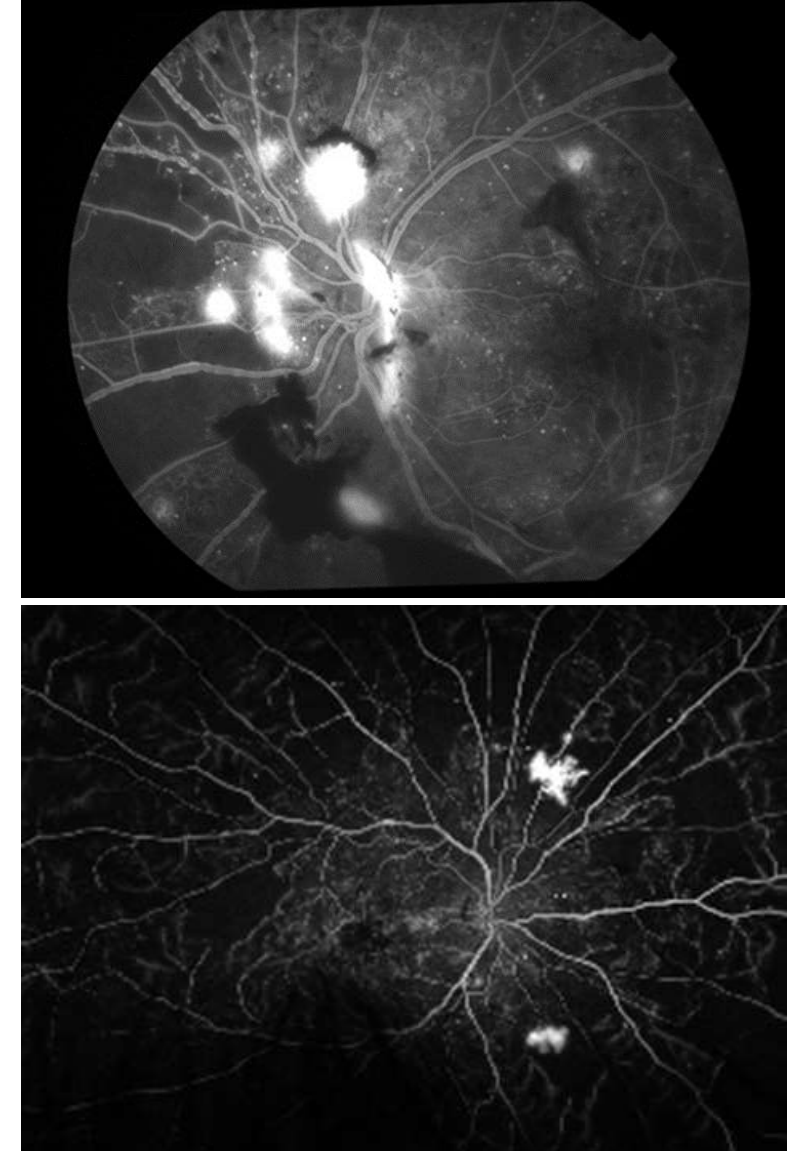
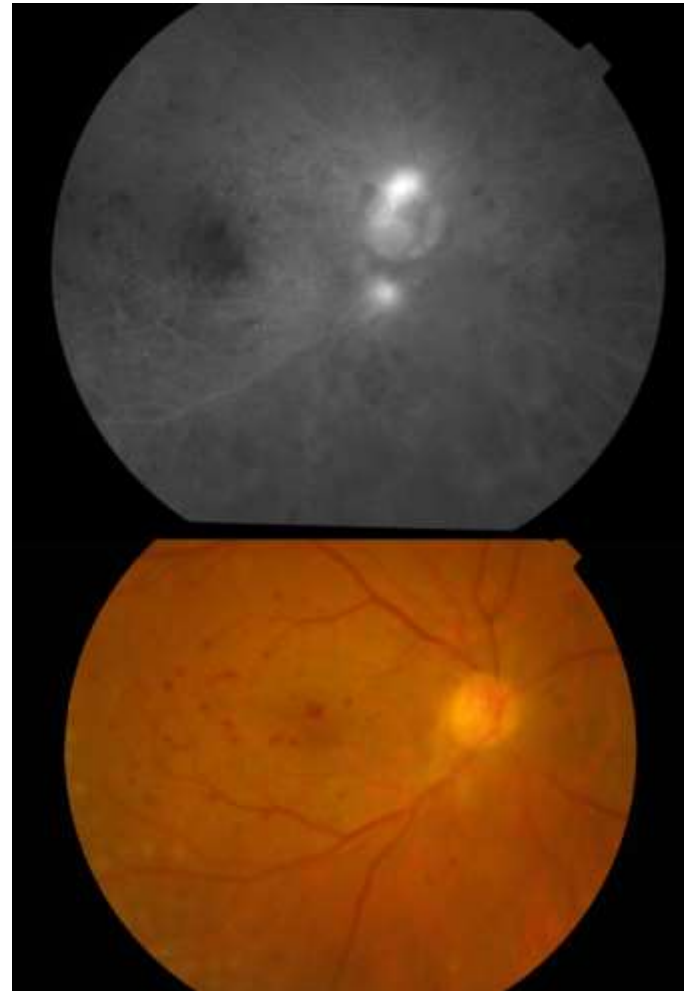
Fundus fluorescein angiography



Ischaemic maculopathy

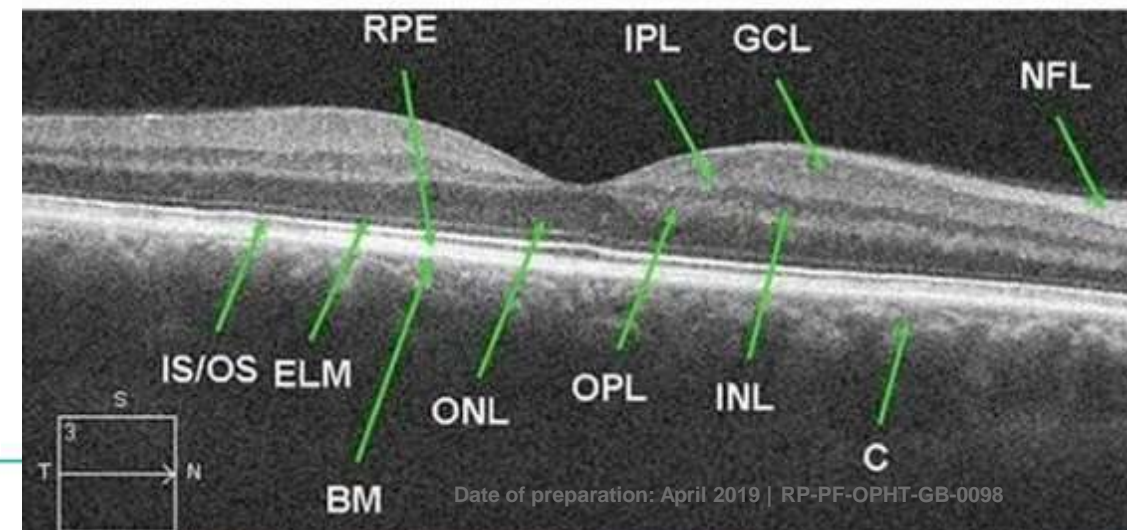
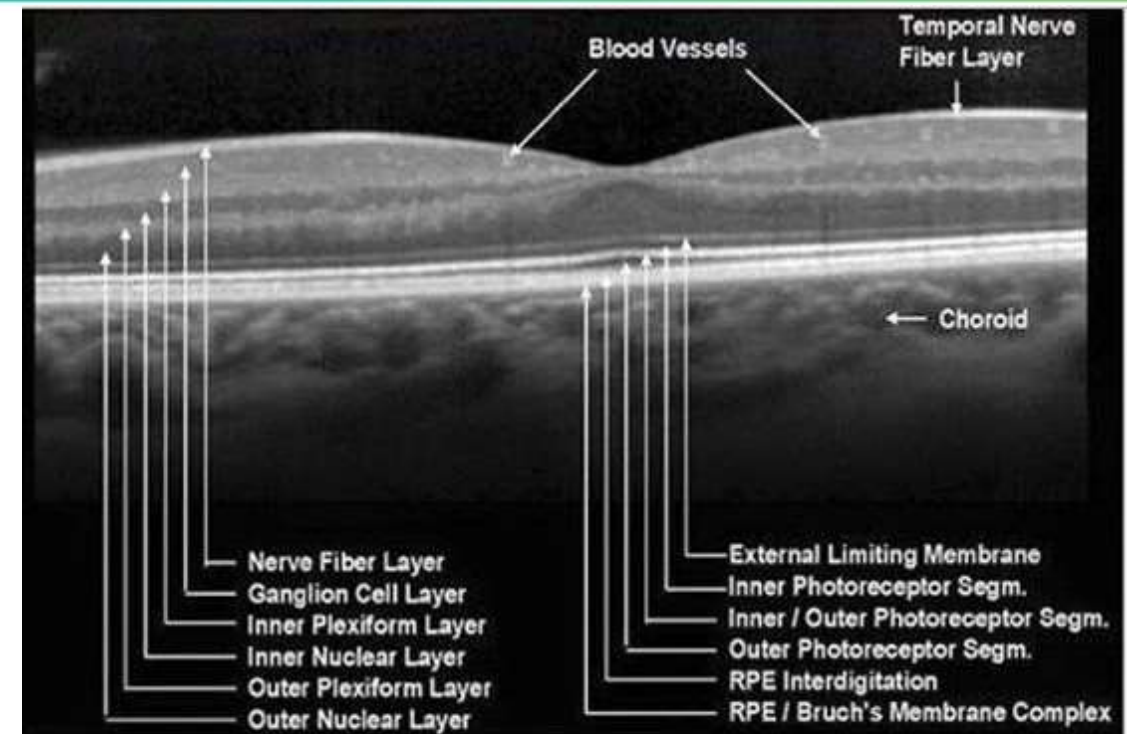
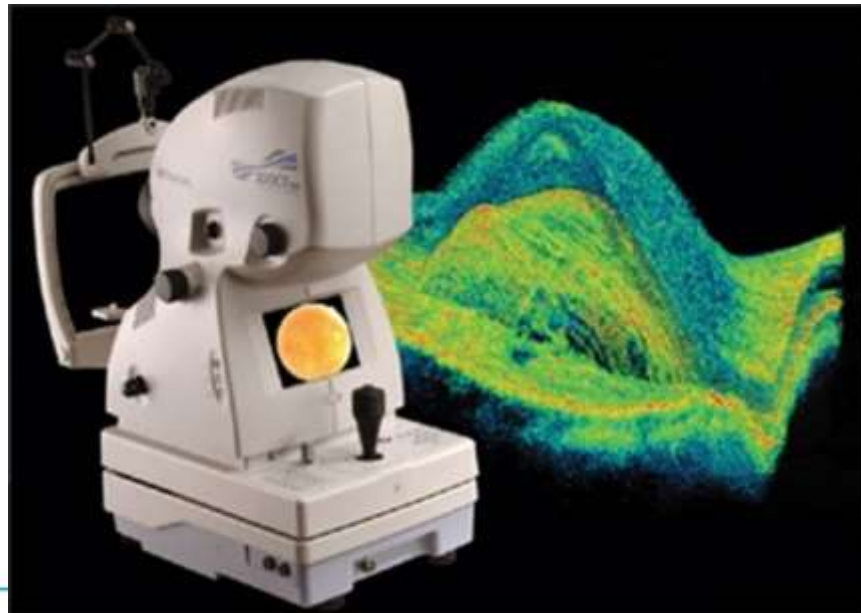


New Vessels (NVD/ NVE)

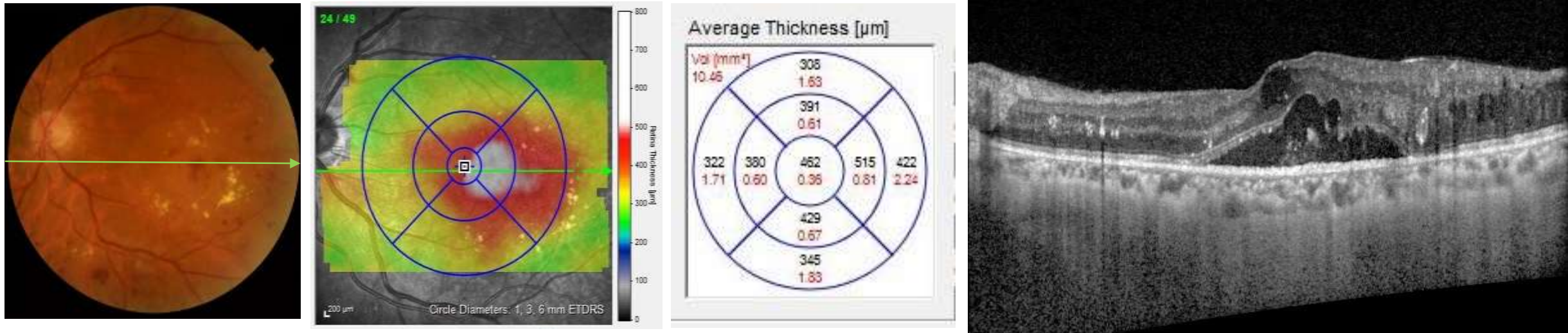


Spectral domain OCT scanning

- Non-invasive test that uses light waves to take cross-sectional pictures of your retina.



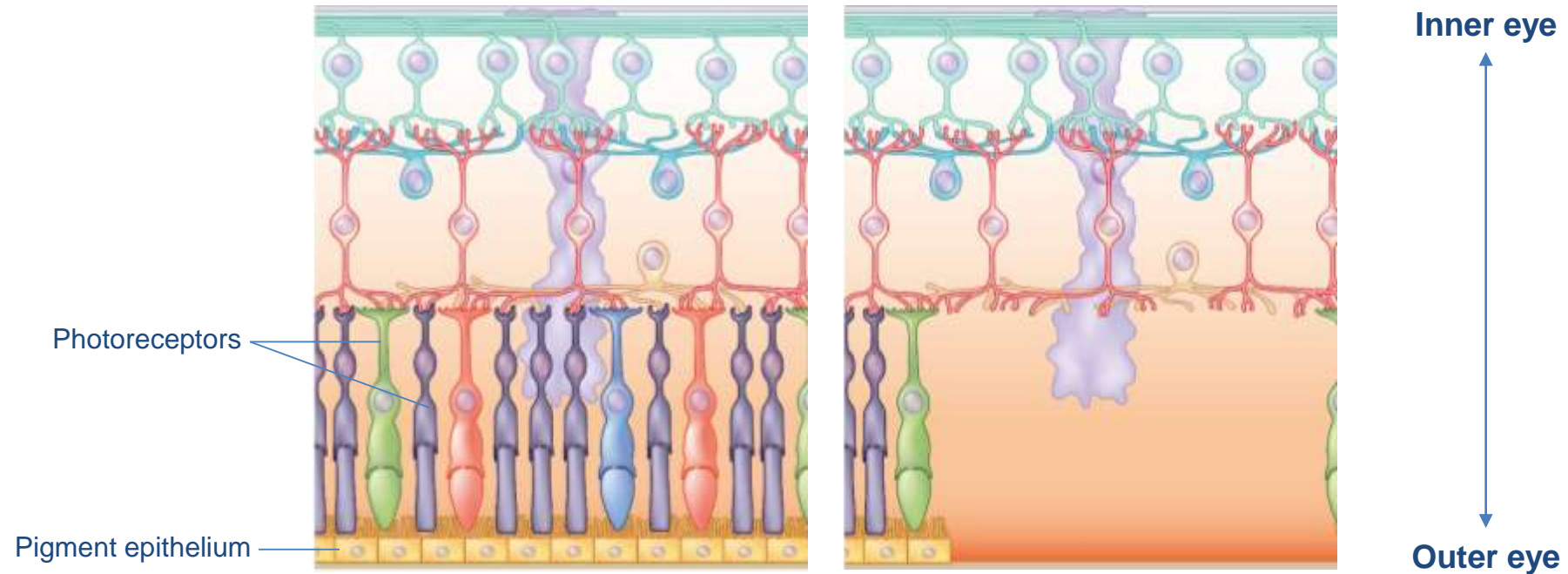
DMO >400 microns



- Consider Anti-VEGF therapy



Diabetic eye disease Treatment of Proliferative Diabetic Retinopathy and Diabetic Macula Oedema



- PRP destroys pigment epithelium and oxygen-consuming photoreceptors¹
- Overall oxygen demand of the retina is reduced, leading to reduced VEGF production
- Role of PRP in ischaemia is controversial – steroids and anti-VEGF agents can reduce oedema without destroying photoreceptors²

Focal/macular grid photocoagulation in DMO

Mainstay of treatment for DMO
since ETDRS¹

Effective in preventing further vision loss

Conventional laser (as used in the
ETDRS) associated with various
ocular side effects, including:²

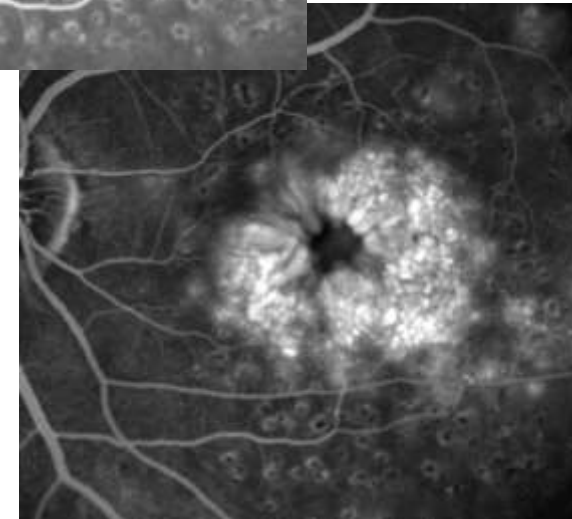
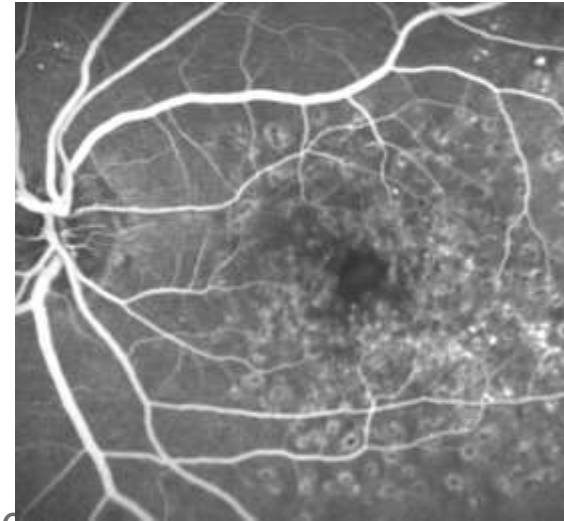
Laser burn scarring

Vision loss

Laser techniques have since evolved to avoid
collateral damage to healthy retina, and to improve
accuracy and treatment time^{3,4}

Subthreshold diode micropulse laser

PASCAL laser



Argon laser burns

Images courtesy of Louise Downey.

1. Ford JA, et al. *BMJ Open*. 2013;3:e002269; 2. Luttrull JK, et al. *Curr Diabetes Rev*. 2012;8:274–284; 3. Gibson JM. Diabetic Retinopathy. Dodson PM (ed.). Oxford University Press; 2008; 4. Lock J H-G, Fong KCS. *Clin Exp Optom*. 2011;94(1):43–51.

What are the current treatment options for DMO?



What are the current treatment options for DMO?

Laser

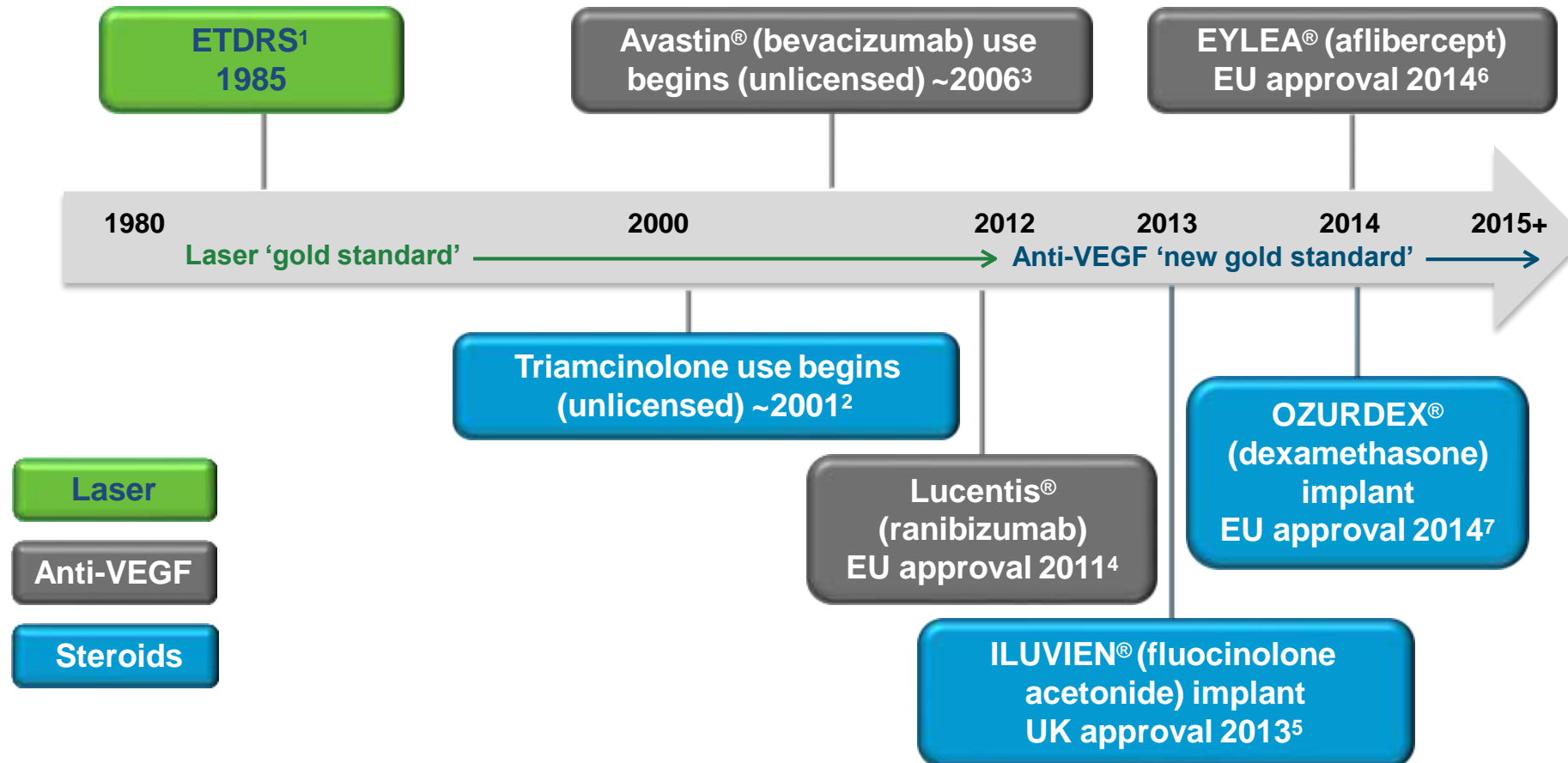
Steroid

Anti-VEGF

Vitrectomy

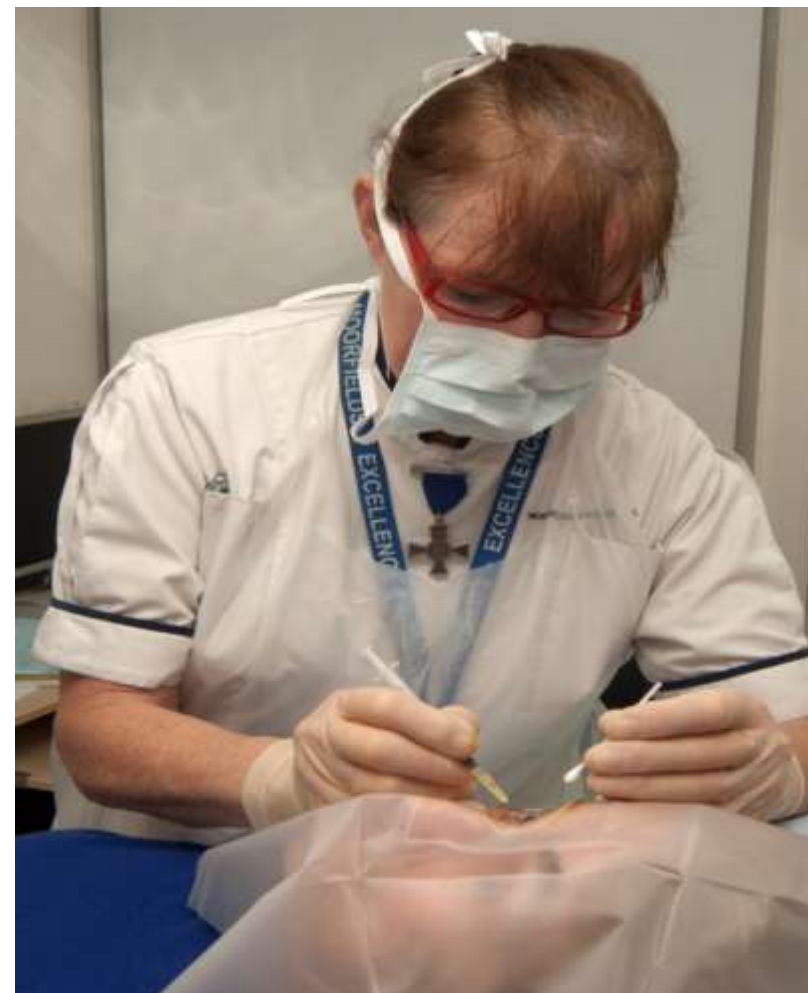
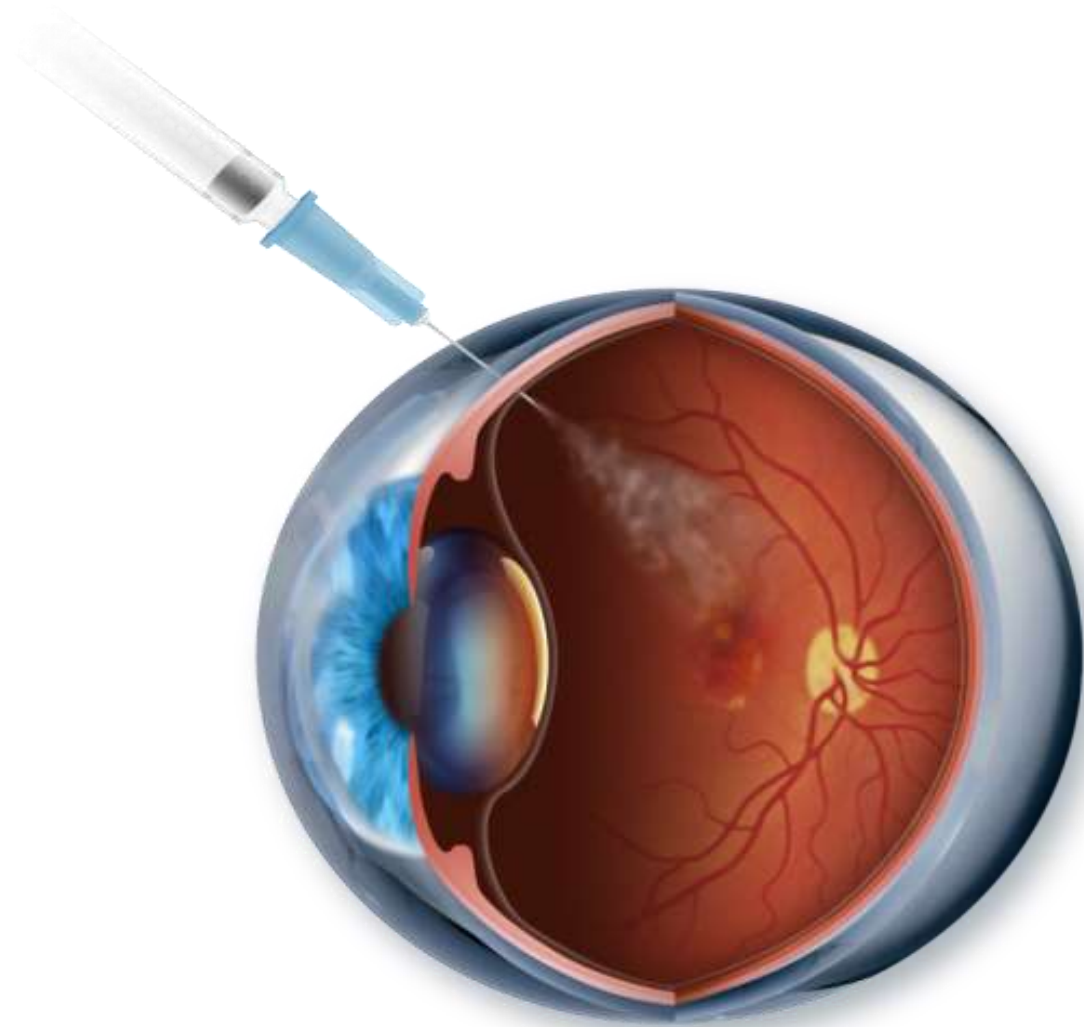
Systemic
control





1. Early Treatment Diabetic Retinopathy Study Research Group. Arch Ophthalmol. 1985;103:1796–1806; 2. Ciulla TA. Review of Ophthalmology. 20 February 2009; 3. Diep TM, Tsui I. Diabetes Res Clin Pract. 2013;100(3):298–305; 4. Genentech. <http://www.genengnews.com/gen-news-highlights/ec-clears-novartis-lucentis-for-diabetic-macular-edema/81244487/>; 5. Alimera Sciences. <http://investor.alimerasciences.com/releasedetail.cfm?releaseid=793994>; 6. Regeneron. <http://newsroom.regeneron.com/releasedetail.cfm?ReleaseID=865393>; 7. European Medicines Agency EPAR summary for Ozurdex (dexamethasone). 2014.

Nurse delivered intravitreal therapy



Rationale for anti-VEGF treatment in DMO

Macular laser photocoagulation was historical standard of care for DMO^{1,2}

Mainstay in stabilising vision

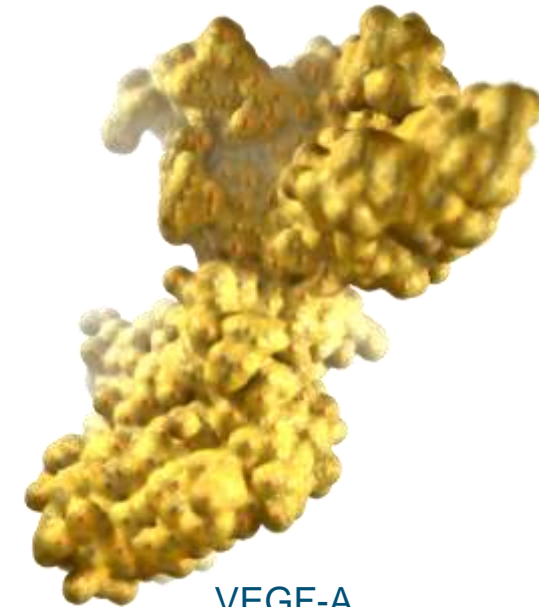
Has demonstrated some success in improving vision

Steroid treatment has demonstrated efficacy in improving vision²⁻⁴

Cataracts and increased IOP are important adverse events to consider

Iluvien® is recommended for patients with recalcitrant DMO and in pseudophakic eyes

Identification of VEGF-A as an important pathophysiological mediator of DMO suggested that anti-VEGF-A therapy might improve vision³



VEGF-A



Ophthalmology
Focused on you

Bayer Ophthalmology Masterclass Programme

Anti-VEGF treatment for DMO

Treatments for DMO

Summary: Anti-VEGF for the treatment of DMO

- Greater improvements in VA compared with laser or sham
- Considered the new 'gold standard' for eyes with centre-involving macular oedema and reduced vision
- CHALLENGES
 - Intravitreal injection is an invasive procedure that is associated with a risk of serious complications such as endophthalmitis
 - Oedema may persist despite monthly treatment
 - High costs are associated with licensed anti-VEGF treatment

Treatment of centre-involving maculopathy: Anti-VEGF/ Steroid injections¹⁻⁶

Anti-VEGF injections

- Aflibercept (Eylea)
- Ranibizumab (Lucentis)

Steroid implants

- Dexamethasone (Ozurdex)
- Fluocinolone (Iluvien)

NICE

If CMT $\geq 400 \mu\text{m}$

SMC

BCVA ≤ 75 ETDRS
letters at baseline

NICE and SMC

If pseudophakic

NICE = National institute for health and care excellence; SMC = Scottish medicines consortium; CMT = Central macular thickness; BCVA = Best corrected visual acuity; ETDRS = Early treatment diabetic retinopathy study.

1. NICE, Identifying and managing complications in adults with type 1 diabetes, 2017. 2. NICE: Identifying and managing complications in adults with type 2 diabetes, 2018. 3. Scottish Medicines Consortium (SMC), aflibercept, 40mg/mL solution for injection (Eylea®) SMC No. (1003/14). 4. SMC, ranibizumab, 10mg/mL solution for injection (Lucentis®) SMC No. (711/11). 5. SMC, dexamethasone 700 micrograms intravitreal implant in applicator (Ozurdex®) SMC No. (1046/15). 6. SMC, fluocinolone acetonide 190 micrograms intravitreal implant (Iluvien®) SMC No. (864/13).



Ophthalmology
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Steroid treatment for DMO

Treatments for DMO

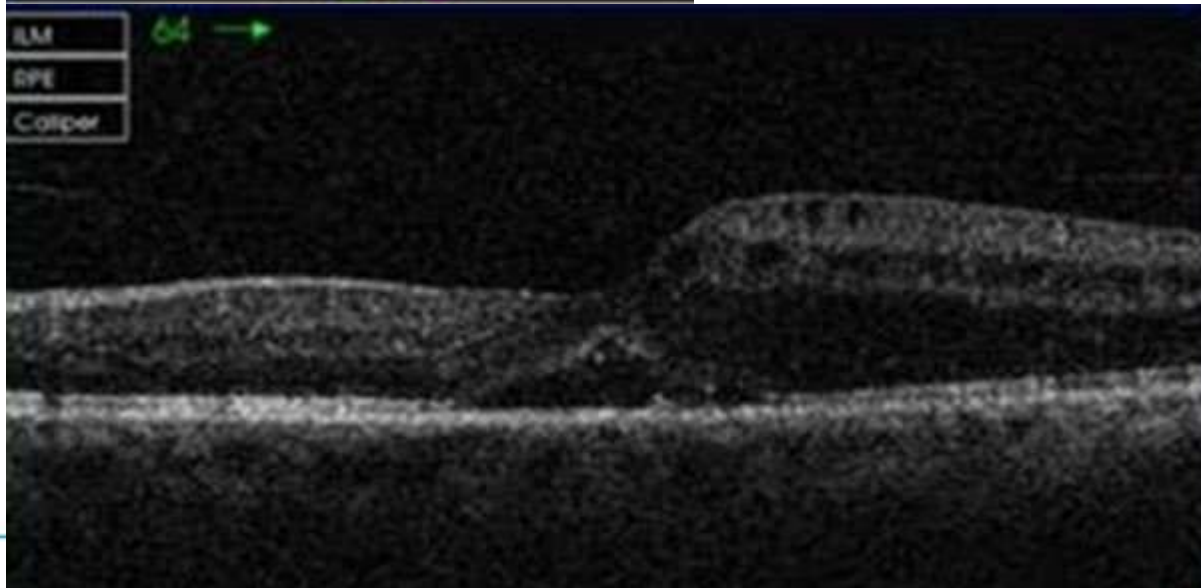
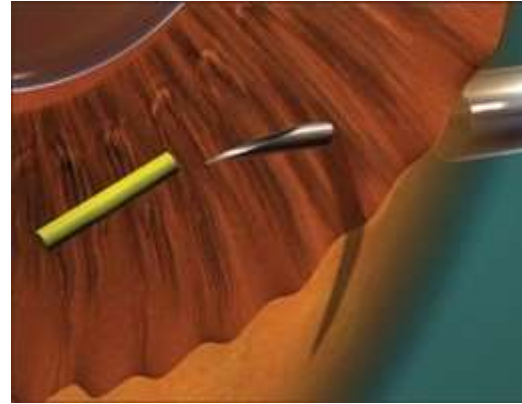
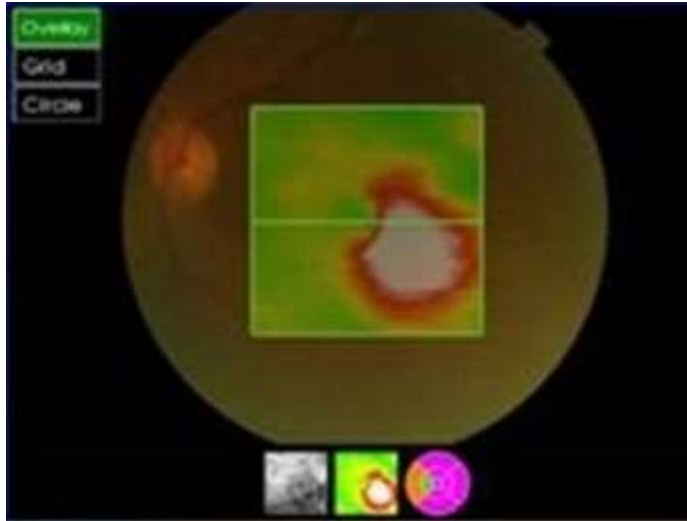
Role of steroids in DMO: overview and approvals

- Reduce the levels of multiple elevated inflammatory factors, including VEGF¹
- Demonstrated efficacy (alone and in combination with laser) for treating DMO²
- Steroid therapy is most often considered for patients with:³
 - Recalcitrant DMO
 - Pseudophakic eyes
 - Those with recent MI/CVA
- Reduced treatment frequency/lower cost can make steroids appealing^{3,4}
 - Frequency of secondary cataracts and increased IOP are important considerations

Steroid	Products	Administration	Dose frequency	Approval status
Triamcinolone acetonide ⁵	Kenalog®	Intravitreal steroid injection	Up to 3 months	Unapproved for intraocular use
Dexamethasone ^{6,7} (DEX)	Ozurdex®	Intravitreal steroid injection	6 months	EU approved
Fluocinolone acetonide ⁸ (FA)	Iluvien®	Extended-release steroid implant	2–3 years	EU approved Recommended in UK ⁹

1. Funatsu H, et al. *Ophthalmology*. 2009;116(1):73–79; 2. Schwartz SG, et al. *Curr Ophthalmol Rep*. 2013;1(3):144–149; 3. The Royal College of Ophthalmologists. Diabetic Retinopathy Guidelines. 2012; 4. Smiddy WE. *Ophthalmology*. 2011;118(9):1827–1833. 5. Yilmaz T et al. *Ophthalmology*. 2009;116(5):902–911. 6. Ford JA et al. *BMJ Open*. 2013;3(3):1–58. 7. Allergan, Ozurdex Summary of Product Characteristics. November 2018. 8. Medicines and Healthcare Products Regulatory Agency (MHRA). Iluvien MHRA Public Assessment Report. 2012. 9. NICE technology appraisal guidance 301.

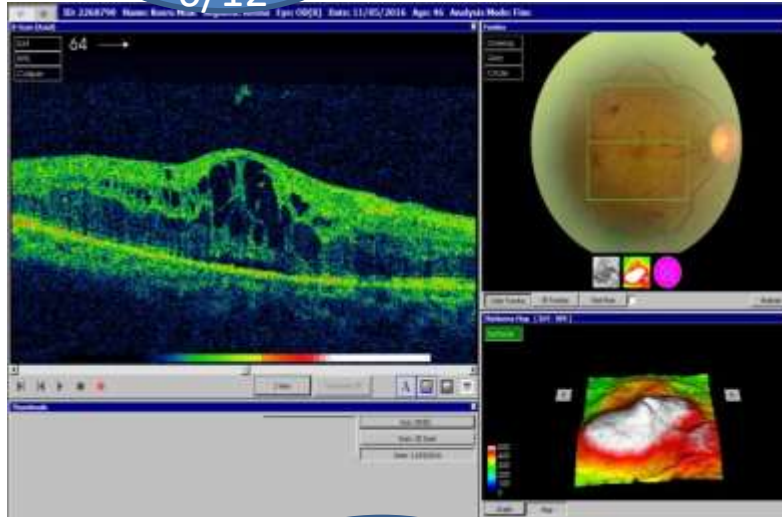
When to consider a steroid implant?



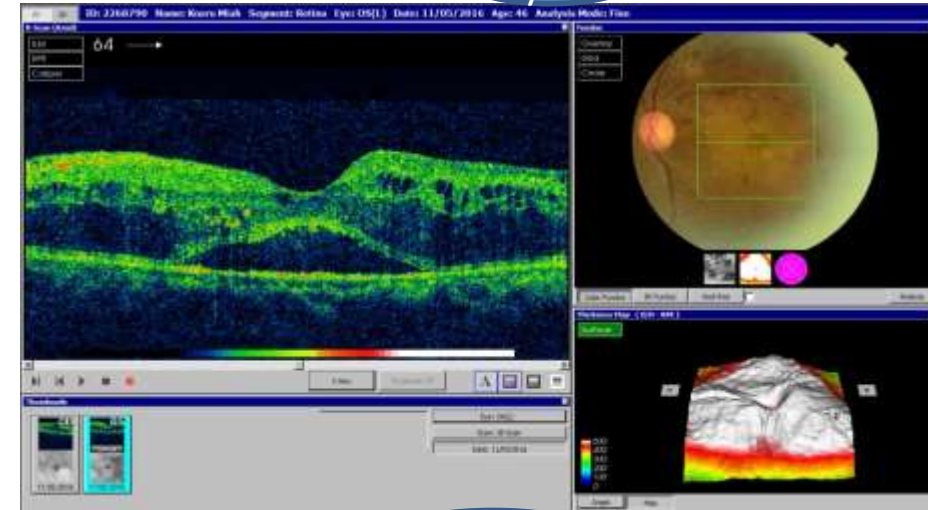
- Poor/no response to anti-VEGF
- In pseudophakic patients
- In patients with recent MI/CVA
- Patient travelling and unable to attend monthly
- In patients WITHOUT glaucoma
- In patients with previous vitrectomy
- ??pregnancy

DMO Management Plan and response

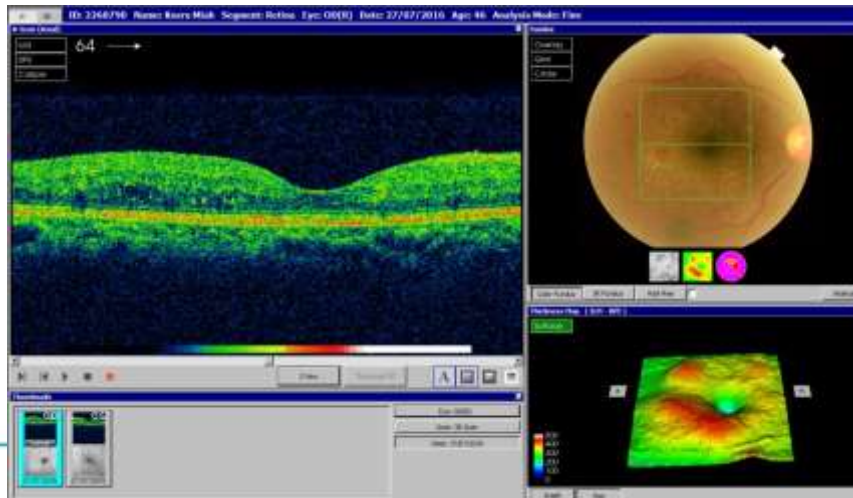
BCVA
6/12



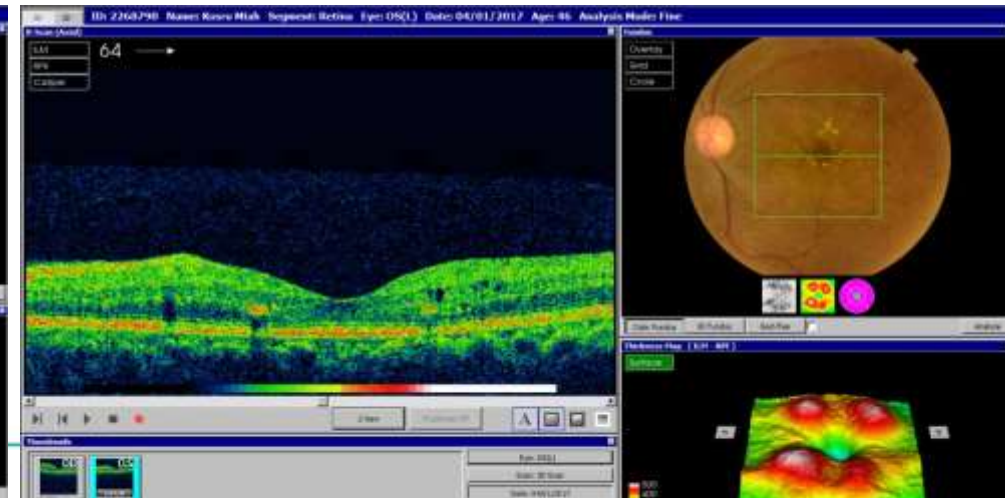
BCVA
6/18



BCVA
6/9



BCVA
6/9



On Predicting the Future

Prediction is very difficult, especially about the future.

Niels Bohr (1885-1962)

The best way to predict the future is to invent it.

Alan Kay

Thank you for listening and your attention
a.mapani@nhs.net